

Biophysical matrix cues from the regenerating niche direct muscle stem cell fate in engineered microenvironments.

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Public Summary:

Skeletal muscle stem cells (MuSCs) are required for quick and effective muscle repair, making MuSCs promising therapeutic targets for tissue engineering and regenerative medicine. The environment MuSCs live in impacts their behavior. Muscles push and pull, giving mechanical cues to MuSCs, however how these mechanical cues affect how well MuSCs can rebuild tissues is unknown. We created a hydrogel that can be softened or stiffened on demand. Soft hydrogels, mimicking healthy muscle promote MuSC activation and expansion, while stiff hydrogels impair MuSC proliferation and arrest myogenic progression. Different structural and soluble cellular factors present in the MuSC environment can exacerbate or mitigate this effect. The cellular response to a stiff microenvironment is fixed within the first three days of culture, as subsequent softening back to a healthy stiffness did not rescue MuSC proliferation or myogenic progression. These results highlight the importance of temporally controlled biophysical and biochemical cues in regulating MuSC fate that can be harnessed to improve regenerative medicine approaches to restore skeletal muscle tissue.

Scientific Abstract:

Skeletal muscle stem cells (MuSCs) are essential for efficacious muscle repair, making MuSCs promising therapeutic targets for tissue engineering and regenerative medicine. MuSCs are presented with a diverse and temporally defined set of cues from their microenvironment during regeneration that direct stem cell expansion, differentiation, and return to quiescence. Understanding the complex interplay among these biophysical and biochemical cues is necessary to develop therapies targeting or employing MuSCs. To probe the role of mechanical cues presented by the extracellular matrix, we leverage chemically defined hydrogel substrates with controllable stiffness and adhesive ligand composition to characterize the MuSC response to matrix cues presented during early and late phases of regeneration. We demonstrate that relatively soft hydrogels recapitulating healthy muscle stiffness promote MuSC activation and expansion, while relatively stiff hydrogels impair MuSC proliferation and arrest myogenic progression. These effects are seen on soft and stiff hydrogels presenting laminin-111 and exacerbated on hydrogels presenting RGD adhesive peptides. Soluble factors present in the MuSC niche during different phases of regeneration, prostaglandin E2 and oncostatin M, synergize with matrix-presented cues to enhance stem cell expansion on soft substrates and block myogenic progression on stiff substrates. To determine if temporally varied matrix stiffness reminiscent of the regenerating microenvironment alters MuSC fate, we developed a photoresponsive hydrogel system with accelerated reaction kinetics that can be rapidly softened on demand. MuSCs cultured on these materials revealed that the cellular response to a stiff microenvironment is fixed within the first three days of culture, as subsequent softening back to a healthy stiffness did not rescue MuSC proliferation or myogenic progression. These results highlight the importance of temporally controlled biophysical and biochemical cues in regulating MuSC fate that can be harnessed to improve regenerative medicine approaches to restore skeletal muscle tissue.

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